94. The nucleic acid of claim 57, wherein the functional domain is heterologous with respect to the two nucleic acid-binding domains.

95. The nucleic acid of claim 68, wherein the activation domain is heterologous with respect to the two nucleic acid-binding domains.

96. The method of claim 76, wherein the functional domain is heterologous with respect to the two nucleic acid-binding domains.

97. The nucleic acid of claim 40, which encodes a chimeric protein which binds the composite binding site that is not a naturally-occurring binding site of a naturally-occurring transcription factor.

98. The nucleic acid of claim 66, which encodes a chimeric protein which binds the composite binding site that is not a naturally-occurring binding site of a naturally-occurring transcription factor.--

Remarks

Claims 40-88 are pending. Claim 71 has been canceled. Claims 40-58, 63, 65-73, 75-77, and 81-84 have been amended. New claims 89-98 have been added. Support for the claim amendments and new claims can be found throughout the specification and in the claims as originally filed. No new matter has been added.

Cancellation and/or amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation and/or amendments to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Disclosure of Nucleotide and Amino Acid Sequences

The Examiner states that the application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821 (a)(1) and (a)(2), but that the application fails to comply with the requirements of 37 C.F.R. §1.821 (d).

Applicants respectfully submit that, responsive to the Examiner's Communication dated June 19, 1998 (Paper No. 16), Applicants submitted on August 19, 1998, a paper copy and computer readable form of a substitute Sequence Listing and a Statement under 37 C.F.R. § 1.821 (f) and (g). A copy of receipt date stamped return postcard indicating that the substitute Sequence Listing was received by the U.S. Patent and Trademark Office on August 24, 1998 is enclosed herein. The substitute Sequence Listing includes all nucleotide and amino acid sequences encompassed by the definition for nucleotide and or amino acid sequences set forth in 37 C.F.R. §1.821 (a)(1) and (a)(2), including the sequences set forth in the figures.

Accordingly Applicants have complied with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825.

Rejection of claims 42-54 and 81-84 under 37 C.F.R. § 112, first paragraph

The Examiner has rejected claims 42-54 and 81-84 under 37 C.F.R. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

It is the Examiner's position that "with regard to claims 42, 46-47, 51-54 and 81, 'variant(s)' of different domains that are set forth in the claim are also claimed", but that "[h]owever, the application as filed does not describe variants of these domains in any fashion."

Applicants submit that the claims were amended and that the newly amended claims do not recite "variants" and therefore the rejection is moot. The claim amendments were done merely to expedite prosecution of the application. Applicants respectfully submit that the specification does describe variants, including mutants, of naturally-occurring (or wild-type) DNA-binding domains (see, e.g., at page 7, lines 18-25).

Rejection of claims 40-65, 72-74, and 81-84 under 37 C.F.R. § 112, second paragraph

Claims 40-65, 72-74, and 81-84 have been rejected under 37 C.F.R. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

In particular, the Examiner states that in regard to claim 40, the use of "distinct families" renders the claim vague and indefinite because the metes and bounds of what constitutes such families

in this context are unclear. Applicants respectfully submits that claim 40 has been amended, and as amended, the claim does not recite "distinct families," thereby obviating the rejection. However, Applicants submit that the specification teaches and the art clearly recognizes that DNA binding domains fall into distinct structural families. The Examiner's attention is drawn, e.g., to Mitchell et al. (Ref. S) and Harrison (Ref. T) cited by the Examiner in the Office Action.

The Examiner states that there is no positive antecedent for "the nucleic acid binding domain" in claim 41. The claim was amended and as newly amended does not recite "nucleic acid binding domains." Thus, the rejection should be withdrawn.

With regard to claim 42, the Examiner indicates that the use of "and variants thereof" renders the claim vague and indefinite. Although Applicants respectfully traverse the rejection, claim 42 has been amended, solely for the purpose of expediting prosecution of the application.

The Examiner states that there is no antecedent basis for "the zinc finger domain" in claim 48. The dependency of claim 48 has been amended, providing proper antecedent basis.

Claim 72 has been amended to correct for the typographical error pointed out by the Examiner. Claim 73 has also been amended by adding the term "further" as suggested by the Examiner.

Accordingly, the rejection of claims 40-65, 72-74, and 81-84 under 37 C.F.R. § 112, second paragraph should be withdrawn.

Rejection of claims 40-43, 51-59, 65-68, and 71-72 under 37 C.F.R. § 102(b)

Claims 40-43, 51-59, 65-68, and 71-72 have been rejected under 37 C.F.R. § 102 (b), as being anticipated by Brugnera et al. *FEBS Letters*, 314:361 (1992). Applicants respectfully traverse this rejection.

Claim 71 has been canceled. Claim 40 and claims 42-43, 51-59, 65, and 72 dependent therefrom are drawn to a nucleic acid encoding a chimeric protein which binds to a nucleic acid comprising a composite binding site, the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein only one of two nucleic acid-binding domains includes a zinc finger motif. Claim 66 and claims 67-68 dependent therefrom are drawn to a nucleic acid encoding a chimeric protein which binds to a nucleic acid comprising a composite binding site, the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite

binding site, and wherein only one of the two nucleic acid-binding domains is a DNA binding domain from a homeodomain containing protein

Brugnera et al. is cited as teaching "a nucleic acid encoding a chimeric protein comprising a POU-specific DNA-binding domain, an Antp homeodomain, and a third domain (comprising an activation domain from Oct-2 POU, because only the homeodomain part of Oct-2 was replaced) linking the two (Figure 1, throughout the reference)."

A claim is anticipated by a reference only if each and every element of the claim is taught by the reference. Brugnera et al. teach a chimeric protein comprising a POU-specific DNA-binding domain and an Antp homeodomain. It is the Examiner's position that "[t]he chimeric protein recognizes both Antp and octamer binding sites, suggesting that each domain contributes to DNA binding specificity (page 361, column 2; page 362, column 2) and thus would bind to a different composite binding site with higher affinity than to the separate binding sites."

Applicants respectfully submit that Brugnera et al. fail to teach a nucleic acid encoding a chimeric protein comprising a zinc finger motif. Thus, since Brugnera et al. fail to teach each and every element of claim 40 and claims 42-43, 51-59, 65, and 72 dependent therefrom, Brugnera et al. does not anticipate these claims.

Similarly, Brugnera et al. fail to teach a nucleic acid encoding a chimeric protein which comprises two nucleic acid-binding domains, wherein only one of the two nucleic acid-binding domains includes a nucleic acid binding domain from a homeodomain containing protein. Thus, since Brugnera et al. fail to teach each and every element of claim 66 and claims 67-68 dependent therefrom, Brugnera et al. does not anticipate these claims.

Thus, Applicants respectfully request that the rejection of claims 40-43, 51-59, 65-68, and 72 under 37 C.F.R. § 102 (b), as being anticipated by Brugnera et al., be reconsidered and withdrawn.

Rejection of claims 40-72 under 37 C.F.R. § 103 (a) in view of Park et al., Mitchell et al., Harrison et al., and Schultz et al.

Claims 40-72 have been rejected under 37 C.F.R. § 103 (a) as being unpatentable over Park et al. (*PNAS* 89: 9094 (1992)), in view of Mitchell et al. (*Science* 245:371 (1989)), Harrison et al. (*Nature* 353:715 (1991)), and Schultz et al. (*Nature* 240: 426 (1988)). Applicants respectfully traverse this rejection.

Claim 71 has been canceled. Claim 40 and claims 41-65, and 72 dependent therefrom are drawn to a nucleic acid encoding a chimeric protein which binds to a nucleic acid comprising a

composite binding site, the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein only one of the two nucleic acid-binding domains includes a zinc finger motif." Claim 66 and claims 67-70 dependent therefrom are drawn to a nucleic acid encoding a chimeric protein which binds to a nucleic acid comprising a composite binding site, the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein only one of the two nucleic acid-binding domains is a nucleic acid-binding domain from a homeodomain containing protein.

Park et al. is relied on by the Examiner as teaching "a general strategy for designing proteins to recognize specific DNA-binding sites" and that "[t]his technique creates a protein that recognizes the composite site (page 9094, column 1)." The Examiner indicates that Park et al. "do not teach to specifically use the DNA-binding domains from distinct families of nucleic acid binding domains, use of specific types of domains such as zinc-finger domains."

Mitchell et al. is relied on by the Examiner as teaching that "different DNA binding transcription factors are composed of a surprising variety of usually separable DNA binding and transcriptional activation domains (page 372, column 2)."

Harrison is relied on as teaching that "many DNA-binding proteins recognize specific sites through small, discrete domains and that these domains can be interchanged between proteins, showing that these domains are independent folded units."

Schultz et al. is relied on as teaching that "enzymes can be created by adding or replacing entire binding or catalytic domains to generate hybrid enzymes with novel specificities" and that "[s]elective fusion of nucleic acid-specific binding domains may produce sequence-specific DNA or RNA cleaving enzymes (page 431, column 1)."

It is the Examiner's position that

> [i]t would have been obvious to one of skill in the art at the time the invention was made to use the various DNA binding domains, activation domains, and cleavage domains taught by Mitchell et al., Harrison, and Schulz in the general strategy for designing proteins to recognize specific DNA-binding sites taught by Park et al. because Park et al. teach that it is within the ordinary skill in the art to stitch the DNA binding domains together from any proteins that recognize a specific DNA sequence by binding along the major groove, to recognize a composite site and Mitchell et al., Harrison, and Schultz teach such domains that can be functionally separated and recombined with other domains.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Applicants respectfully submit that Park et al., Mitchell et al., Harrison, and Schultz fail to provide any motivation to combine the cited references that would be within the skill in the art at the time the application was filed. Park et al. fail to provide any evidence that the combination of DNA binding domains from two different DNA binding domains or of DNA binding domains which do not occur together in the same protein, or in the same order and/or with the same spacing as in the protein in nature, would bind to a composite binding site. Neither of the secondary references, nor the knowledge in the art at the time the invention was made, cure this defect. In fact, none of the cited secondary references teach chimeric DNA binding proteins. Thus, a person of skill in the art would not find sufficient motivation to combine the teachings of the references.

Furthermore, Applicants respectfully submit that even if there was sufficient motivation to combine the references, there was no reasonable expectation of success. As set forth above, Park et al. teach cross-linking of two identical DNA binding domains of proteins which naturally form a homodimer that binds to a DNA binding site. Park et al. do not teach that the combination of DNA binding domains from two different DNA binding domains or of DNA binding domains which do not occur together in the same protein, or in the same order and/or with the same spacing as in the protein in nature, would bind to a composite binding site. Applicants were the first to demonstrate that the combination of two different types of DNA binding domains which do not occur together in the same protein in nature, resulted in a composite DNA binding domain which binds to a composite DNA binding site and activates transcription *in vivo* (see Examples).

Lastly, the cited references fail to teach or suggest all the claim limitations. As set forth above, neither Park et al., nor Mitchell et al., Harrison and Schultz fail to teach a nucleic acid encoding a chimeric DNA binding protein.

Thus, in view of all of the above, Applicants respectfully request that the Examiner reconsider and withdraw rejection of claims 40-72 under 37 C.F.R. § 103 (a) as being unpatentable over Park et al., in view of Mitchell et al., Harrison et al., and Schultz et al.

Rejection of claims 40-88 under 37 C.F.R. § 103 (a) in view of Park et al., Mitchell et al., Harrison et al., Schultz et al. and Gossen et al.

Claims 40-88 have been rejected under 37 C.F.R. § 103 (a) as being unpatentable over Park et al. (*supra*), in view of Mitchell et al. (*supra*), Harrison et al. (*supra*), Schultz et al. (*supra*) as applied to claims 40-72 above, and further in view of Gossen et al. (U.S. Patent No. 5,464,758). Applicants respectfully traverse this rejection.

Claim 71 has been canceled. Claim 40 and claims 41-65, and 72-74 dependent therefrom are drawn to a nucleic acid encoding a chimeric protein which binds to a nucleic acid comprising a composite binding site, the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein only one of the two nucleic acid-binding domains includes a zinc finger motif. Claim 66 and claims 67-70 dependent therefrom are drawn to a nucleic acid encoding a chimeric protein which binds to a nucleic acid comprising a composite binding site, the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein only one of the two nucleic acid-binding domains is a nucleic acid-binding domain from a homeodomain containing protein. Claims 75-83 and 84-89 are drawn to a method for modulating expression of a gene in a cell, comprising modulating the level of a chimeric protein in a cell which includes a gene operably to a composite binding site to which the chimeric protein binds, wherein the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site.

Park et al., Mitchell et al., Harrison and Schultz are relied upon by the Examiner as disclosing what is summarized in the previous section. Gossen et al. is relied upon by the Examiner as teaching "a nucleotide molecule coding for a chimeric transactivator fusion protein comprising a DNA binding domain (tet repressor binding domain) and a transactivation domain (such as VP16 of HSV)."

It is the Examiner's opinion that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to form a transcriptional regulatory system form the DNA encoding a chimeric transactivation protein made obvious by the teachings of Park et al. (AW2), Mitchell et al. (S), Harrison (T) and Schultz (U), using the method taught by Gossen et al. because Gossen et al. teach that it is within the ordinary skill in the art to make a nucleic acid vector that encodes a chimeric transactivator fusion protein (under the control of a promoter active in eukaryotic cells), make a nucleic acid encoding a heterologous protein operably linked to a regulator binding site that the chimeric protein binds to..."

However, as set forth above, neither Park et al., nor Mitchell et al., Harrison and Schultz provide any motivation to combine the teachings of these references to obtain a nucleic acid encoding

a chimeric DNA binding protein which binds to a nucleic acid comprising a composite binding site, the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site. Gossen fails to cure the defect. In fact, Gossen et al. fail to teach a chimeric DNA binding domain.

Furthermore, even if there was sufficient motivation to combine the references, there was no reasonable expectation of success. Nothing in Gossen et al. indicates that there was a reasonable expectation of success.

Lastly, the cited references fail to teach or suggest all the claim limitations. As set forth above, neither Park et al., nor Mitchell et al., Harrison and Schultz fail to teach a nucleic acid encoding a chimeric DNA binding protein. This defect is not cured by Gossen.

Thus, in view of all of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 40-88 as being unpatentable over Park et al., in view of Mitchell et al., Harrison et al., Schultz et al. and further in view of Gossen et al.

Conclusion

In view of the above remarks and the amendments to the claims, it is believed that this application is in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 832-1000.

Respectfully submitted,

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